Newborn Hearing Screening: The Missing Pieces to the Puzzle

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Three Newborns

Case 1
• Healthy, full term
• Passed NBHS
• 3 months old -- not responding to sounds
• Diagnostic ABR shows Auditory Neuropathy

Case 2
• Healthy, full term
• Passed NBHS
• Hearing loss noted at preschool screening
• Asymmetric hearing loss
• Diagnosed with CMV hearing loss

Case 3
• Healthy, full term
• Refer NBHS
• Moderate hearing loss
• Delayed motor milestones
• Developed loss of night vision
• Diagnosed with Usher syndrome
Overview

• Hearing loss overview
• Current newborn hearing screening: what are we missing
• Genetic hearing loss
• Congenital CMV hearing loss

Take Home Points:
1. Audiometric newborn hearing screening is inexpensive and widely implemented but lacks ability to detect important forms of childhood hearing loss.
2. Genetic testing for deafness is highly sensitive and specific but is currently inhibited by cost and time.
3. Testing for congenital CMV is emerging as a valuable addition to the NBHS.

Congenital Hearing Loss Epidemiology

“Deafness . . . means the loss of the most vital stimulus— the sound of the voice that brings language, sets thoughts astir, and keeps us in the intellectual company of man.”

– Helen Keller

• The most common sensory deficit in humans
• Affects 278 million people worldwide
• 50% of 80-year-olds

Thalassemia 1/25,000
PKU 1/10,000
DMD 1/3,500
Sickle Cell 1/3,000
Spina bifida 1/2,000
Down Syndrome 1/800
Deafness 1/500

Congenital Prevalence
Causes of Congenital Hearing Loss

- Genetic Hearing Loss
  - Non-syndromic
  - Syndromic
  - >100 genes involved
- Environmental Hearing Loss
  - Ototoxic drugs
  - Neonatal hypoxia
  - Infections

Benefits of Early Intervention

- Improved social interactions, quality of life
- Goal is same-track education
- Intervention by < 6 months maintains language, social, and emotional development at the expected level for age

Cochlear Implants Improve Children's Quality of Life

Loy et al 2010
**NBHS: History and Methodologies**

- Pioneered by Downs in 1964
- First implemented in Rhode Island 1989
- Screening tests need to be sensitive and administered by a trained professional
- **Otoacoustic emissions (OAE):** tests function of cochlea
- **Auditory Brainstem Response:** tests function of cochlea and auditory nerve

**NBHS: Current paradigm**

- OAE NBHS prior to discharge from hospital
- Some states: OAE --> automated ABR screening
- REFER x 2: confirmatory testing with ABR
- Goal is:
  - Diagnosis by 3 months
  - Intervention by 6 months
NBHS: Advantages/Disadvantages

Advantages
• Fast result
• Non-invasive
• Low cost
• Easily administered

Disadvantages
• Poor sensitivity for specific forms of HL
• Low specificity
• High false positive rate
• Not an etiological diagnosis

NBHS: What are we missing?

1. Auditory neuropathy
2. Later onset genetic/CMV hearing loss
3. Mild/moderate loss
4. Diagnosis of syndromic hearing loss

1,119 Individuals with Hearing Loss

Sloan-Heggen et al 2016
Genetic Hearing Loss

- **Congenital hearing loss – 1 in 500**
  - **Environmental causes (20%)**
    - Congenital CMV
    - Ototoxicity
    - Hypoxia
  - **Genetic causes (80%)**
    - **Syndromic (30%)**
      - Usher Syndrome
      - Pendred Syndrome
      - Waardenburg Syndrome
      - BOR Syndrome
    - **Non-Syndromic (70%)**
      - **Recessive (80%)**
      - **Dominant (19%)**
        - Mitochondrial, miRNA & X-linked (<1%)

Hearing loss is genetically heterogeneous:

- 80 genes
- 30 genes
- 6 genes
- >100 total genes
- >6000 reported mutations

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Genetic testing for hearing loss

Genetic diagnosis in 440 patients (Sloan-Heggen et al 2016)

Meaningful genetic testing requires comprehensive genetic testing

**Massively Parallel Sequencing for Genetic Diagnosis of Hearing Loss: The New Standard of Care**

A. Elliot Shearer, MD, PhD¹, and Richard J. H. Smith, MD²,³

[SAGE]
Genetic Testing: Advantages/Disadvantages

Advantages
• Highly specific
• Etiological diagnosis
• Identifies syndromic patients

Disadvantages
• Costly
• Time-consuming (3 month turn around time)

CMV: overview

• Most common congenital infection worldwide
• >30,000 infants/year in US born with cCMV
• $2 billion/year
• Transmission Can occur in utero, at delivery, or postnatally

Congenital Prevalence

- Thalassemia 1/25,000
- PKU 1/10,000
- DMD 1/3,500
- Sickle Cell 1/3,000
- Spina bifida 1/2,000
- Down Syndrome 1/800
- cCMV 1/150
- Deafness 1/500
**CMV Epidemiology**

The spectrum of cCMV

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>“Asymptomatic”?</th>
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</thead>
<tbody>
<tr>
<td>Death</td>
<td>No impairments</td>
</tr>
<tr>
<td>Severe</td>
<td>Cerebral palsy, hearing loss, vision loss</td>
</tr>
<tr>
<td>Moderate</td>
<td>Cerebral palsy, hearing loss, vision loss</td>
</tr>
<tr>
<td>Mild</td>
<td>Cognitive delays, developmental delays, feeding issues, hearing and vision loss</td>
</tr>
<tr>
<td>Profound</td>
<td>Hearing loss, mild vision disorders</td>
</tr>
<tr>
<td>Bilateral</td>
<td>No impairments</td>
</tr>
<tr>
<td>Progressive</td>
<td>No impairments</td>
</tr>
</tbody>
</table>

CMV symptomology is characterized by variability

The spectrum of cCMV

CMV symptomology is characterized by variability
cCMV and Hearing Loss

- **cCMV (1/150 births)**
  - 10% Symptomatic
  - 90% Asymptomatic

- 33% SNHL
- 10% SNHL

- **71% Bilateral**
  - 77% severe to profound
  - 20% delayed onset
  - 18% progressive

- **39% Unilateral**
  - 78% severe to profound
  - 9% delayed onset
  - 20% progressive

Goderis et al 2014

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CMV diagnostic testing

<table>
<thead>
<tr>
<th>Source</th>
<th>Method</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine or Saliva collected</td>
<td>CMV viral culture</td>
<td>- Within 21 days of life</td>
</tr>
<tr>
<td></td>
<td>CMV DNA PCR ($200)</td>
<td>- Preferred</td>
</tr>
<tr>
<td>Blood/plasma/serum</td>
<td>CMV DNA PCR</td>
<td>- Insensitive</td>
</tr>
<tr>
<td></td>
<td>CMV Ab (IgM/IgG)</td>
<td>- Nonspecific</td>
</tr>
<tr>
<td>Dried Blood Spot</td>
<td>CMV DNA PCR</td>
<td>- Insensitive</td>
</tr>
</tbody>
</table>

Result Interpretation

- IgG: negative
  - Not previously CMV infected
  - (at risk for primary infection)
- IgG: positive
  - Recent CMV infection
- IgM: negative
  - Past CMV infection (not recent)
NEW SUBSECTION. 8A. a. If the results of the newborn hearing screening performed under this section demonstrate that the newborn has hearing loss, the birthing hospital, birth center, physician, or other health care professional required to ensure that the hearing screening is performed on the newborn under this section, shall do all of the following:

1. Test the newborn or ensure that the newborn is tested for congenital cytomegalovirus before the newborn is twenty-one days of age.

2. Provide information to the parent of the newborn including information regarding the birth defects caused by congenital cytomegalovirus and early intervention and treatment resources and services available for children diagnosed with congenital cytomegalovirus.

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**CMV Targeted Screening**

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Failed NBHS

- Diagnosis Apparent
  - CMV saliva/urine PCR
    - Positive (<3 weeks of age)
      - cCMV Hearing Loss
    - Positive (>3 weeks of age)
      - Blood Spot CMV testing
        - Positive
          - cCMV Hearing Loss
        - Negative
          - Non-cCMV Hearing Loss
            - Genetic Testing, Further Workup
    - Negative

- Idiopathic Diagnosis
  - MRI brain and CT temporal bone; serial audiologic testing
    - Positive
      - Suspected cCMV Hearing Loss
    - Negative
```

Park et al 2014
On the basis of available evidence, we conclude that each year in the United States as many as several thousand children with congenital CMV could benefit from newborn CMV screening, early detection, and intervention.
Future directions

• Molecular therapy requires a molecular diagnosis

Stem Cell Therapy – Round Window Approach

Gene Transfer – Ex Utero Approach

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Conclusions

• Universal audiometric NBHS has dramatically improved our ability to diagnose and intervene for individuals with congenital hearing loss
• The current NBHS is insensitive to several relatively common types of childhood hearing loss
• Current genetic testing methods are too expensive and time consuming to be part of the NBS
• CMV testing will quickly become an important addition/supplement to the NBHS

Thank you

Richard Smith, MD